>236PRUs for VNP2Y12.
Results: Using univariate logistic regression, several variables were associated with HRPR (anemia, female gender, history of hypertension and absence of a clopidogrel loading dose for LTA, and anemia, female gender, history of hypertension, CVA, diabetes or hypercholesterolemia, kidney disease and concurrent use of proton pump inhibitors for VNP2Y12). On multivariate analysis however, the only variable independently associated with HRPR with both assays was laboratory-defined anemia, present in 37.3% of the patients. The prevalence of HRPR by LTA was 34.3% amongst anemic patients and 15.6% of the patients with normal hemoglobin levels, and 59.8% versus 25.9% respectively by VNP2Y12 ($p<0.005$ in both cases). In a subgroup of 50 patients testing was done both before and after the clopidogrel loading dose. At baseline there were no differences in the platelet aggregation with either assay. The absolute inhibition of platelet aggregation to ADP following the clopidogrel load was significantly less in anemic patients compared to patients with normal hemoglobin levels, as measured by both assays (delta residual aggregation by LTA of 15.8±5.8% vs 28.8±3.2%, $p<0.05$, and delta PRU by VNP2Y12 of 56.5±35.5 PRUs vs 145.0±14.2 PRU's, $p<0.01$ respectively).
Conclusion: Anemia is a novel major contributor to HRPR on clopidogrel and may explain some of the intra-individual variability of platelet aggregation testing.

TCT-162

Ticagrelor Enhances Adenosine-induced Coronary Vasodilatory Responses in Humans—a Randomised, Double-Blind, Placebo-Controlled, Crossover, Single Centre Study Using Transthoracic Color Doppler Echocardiography

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Background: Ticagrelor, the first reversibly binding oral P2Y12 antagonist, has a clinical profile consistent with a secondary pharmacologic effect related to adenosine. This study explored whether ticagrelor can augment increases in coronary blood flow velocity (CBFV) induced by adenosine, and if any increase can be inhibited by theophylline, an adenosine receptor antagonist.
Methods: 40 healthy male subjects (18-40y) underwent 2 treatments, 180mg ticagrelor or placebo, separated by a wash-out. CBFV was measured using transthoracic color Doppler echocardiography. Following 3.5MHz color Doppler mapping of the mid-distal segment of the left anterior descending coronary artery, CBFV was measured using 1.75MHz pulsed wave spectral Doppler. During each treatment period a step wise increased adenosine infusion ladder, 0, 50, 80, 110 and 140μg/kg/min, was given 3x: predose; 2h after administration of 180mg ticagrelor or placebo; after a 20-min infusion of 5mg/kg theophylline. CBFV was measured at each adenosine dose. Complete CBFV signals were obtained in 38/40 subjects.
Results: Adenosine dose-dependently increased CBFV during all dose ladders. Ticagrelor significantly enhanced the adenosine-induced CBFV responses compared to placebo as the area under the CBFV vs adenosine dose curve increased significantly, 15% (CI:9%;21%) vs 4% (CI:-1%;10%); $p=0.008$. The greatest effect on CBFV was observed at 80μg/kg/min adenosine; ticagrelor 72.5±32.9cm/s, placebo 54.0±29.3cm/s. Theophylline inhibited the adenosine-induced vasodilatory responses in a similar way in both groups, indicating the augmented response after ticagrelor dosing was mediated via the adenosine receptors and not through a unique pathway.
Conclusion: Ticagrelor enhanced coronary vasodilatory response by an adenosine-dependent mechanism. This suggests that augmentation of the physiological response to endogenous adenosine may be a mechanism that, together with the primary antiplatelet action, might contribute to the clinical profile of ticagrelor.

TCT-163

Accelerated Platelet Inhibition after Switching with Hydrophilic Statin in Patients with Increased Platelet Reactivity During Atorvastatin and Clopidogrel Coadministration (ACCEL-STATIN) study: a randomized, parallel-group trial

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Background: Because CYP3A4 enzyme activity contributes to clopidogrel metabolism, CYP3A4-metabolized statin may affect the pharmacokinetics and pharmacodynamics of clopidogrel. We performed this study to assess the influence of non-cytochrome (CYP) 3A4-metabolized statin switch on platelet inhibition among patients receiving clopidogrel and atorvastatin coadministration.
Methods: We enrolled 50 patients with increased platelet reactivity [20μM ADP-induced maximal platelet aggregation (PA) >50%] receiving chronic atorvastatin (10mg/d) and clopidogrel (75mg/d) plus aspirin (100mg/d) treatments after percutaneous coronary intervention (PCI) (≥6 months). They were randomly assigned to switch atorvastatin with either rosuvastatin 10 mg/d (n=25) or pravastatin 20 mg/d (n=25). Platelet reactivity was assessed before and after 15-day switch treatment with conventional aggregometry and the VerifyNow P2Y12 assay. Primary endpoint was absolute change of ADP-induced maximal PA. High on-treatment platelet reactivity (HPR) was defined as 5μM ADP-induced maximal PA > 46% or P2Y12 reaction unit (PRU) >235.
Results: All patients completed the study without specific events. Absolute changes of 20 and 5μM ADP-induced maximal PAs were significant after switch with non-CYP3A4-metabolized statin [66.9±8.4% to 60.3±15.0%, mean delta 6.6%, 95% confidence interval (CI) 3.2~10.1%, $p<0.001$; 52.7±10.7% to 46.4±16.7%, mean delta 6.3%, 95% CI 2.5~10.2%, $p<0.001$, respectively). Likewise, ADP-induced late PAs and PRU were significantly decreased after switch ($p \leq 0.002$). HPR was also overcome in about one third of the patients. The magnitude of this effect was similar after the switch with rosuvastatin or pravastatin. Compared with patients who received calcium channel blocker (CCB) (n=9), those who did not take CCB (n=41) showed significantly enhanced antiplatelet effect of clopidogrel.
Conclusion: Among PCI-treated patients with increased platelet reactivity during clopidogrel and atorvastatin coadministration, switch with non-CYP3A4-metabolized statin can enhance the antiplatelet effect of clopidogrel and decrease the risk of HPR, especially in patients without CCB. These results can support pharmacological interactions between clopidogrel and CYP3A4-metabolized drugs.

TCT-164

Impact of Bleedings on Prasugrel Adherence in Real World Patients

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Background: Recent guidelines recommend the use of aspirin and prasugrel in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI). However, prasugrel use has been evaluated only in randomized trials. There are no data regarding prasugrel in the real world setting.
Methods: A total of 298 consecutive patients aged 68±10 years (31% ≥75 years) underwent stent implantation and received prasugrel therapy. Indications to prasugrel therapy were: 1) ST-elevation acute myocardial infarction (STEMI; 41%), 2) drug-eluting stent (DES) implantation in diabetics (24%), 3) stent thrombosis (3%), 4) left main DES implantation (6%), and 5) ACS or DES implantation in patients with high residual platelet reactivity on clopidogrel therapy (26%). All patients received a 60 mg prasugrel loading dose. Patient aged ≥75 years and with ≤60 kg of body weight received a maintenance dose of 5 mg/day (10 mg/day for all the other patients). Follow-up data, including adherence to prasugrel therapy, were collected by telephone interviews or outpatient visits. Minimal follow-up length was 6 months (mean 9±3 months).
Results: Major, minor, and minimal bleedings (TIMI criteria) occurred in 2.7%, 4.7%, and 15.1% of the enrolled patients. The most frequent minimal bleeding event was epistaxis. Only 8 (2.7%) patients permanently discontinued prasugrel therapy due to bleeding events (n=4), possible side effects (n=2), or medical decisions not associated with bleeding or side effects (n=2). Fourteen (4.7%) patients temporarily discontinued prasugrel (average 6.5 days) mainly due to surgical procedures. No definite or probable stent thrombosis occurred, while 3 patients had a de-novo myocardial infarction, and 1 an ischemic stroke. There were 11 deaths, due to heart failure or refractory cardiogenic shock (9), pulmonary embolism (1), and cancer (1).
Conclusion: In the clinical practice, major and minor bleeding event rates associated with prasugrel therapy are comparable with those reported in controlled randomized trials. Minimal bleeding event rate is higher than reported, but it seems not to impact on adherence to treatment.

TCT-165

Response to Prasugrel in ST Elevation Myocardial Infarction Patients: is it as Rapid as we Expected?

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Background: A pre-hospital 60mg loading dose of prasugrel can be administered in patients with ST elevation Myocardial Infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI). Whether such a loading dose of prasugrel is efficient in inhibiting platelet activity when pPCI is started is unknown. Using the P2Y12 Verifynow assay (Accumetrics, San Diego, USA), we assessed prasugrel responsiveness in the beginning of the pPCI in STEMI patients.
Methods: Our study is a single center observational study. During a 6 months period, we prospectively analyzed STEMI patients. We compared this group to Non-STEMI patients (NSTEMI) group, treated in a similar way, with same delay between prasugrel administration and Verifynow assessment. A pre-defined cut-off Platelet Reactivity Unit (PRU) > 235 was considered as suboptimal inhibition.
Results: Forty five STEMI and 20 NSTEMI patients were included. Baseline characteristics were similar in both groups, including the mean time between prasugrel administration and Verifynow assessment (82±36 and 88±51 minutes, respectively, $p=0.97$). Nevertheless, overall prasugrel responsiveness was suboptimal in STEMI patients and lower than in NSTEMI patients, with median PRU of 263[197-291] versus 69[46-118], respectively ($p<0.00001$). In STEMI group, 64.4% had PRU>235 versus 20% in NSTEMI group ($p<0.003$). We confirmed STEMI patients were good prasugrel responder, in a chronic phase, more than 30 days after the first test, with median PRU of 85[47-126]. In STEMI group, no parameter was found to be significantly correlated to this slow responsiveness to prasugrel; there was a trend with morphine use (OR=